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A Bibliometric Analysis of Iminosugars-related Studies

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This work aims to analyze the literature on iminosugars-related studies from a bibliometric perspective. The outcomes from a bibliometric analysis help to provide an overview of the research topic and an understanding of the current trend in the study to justify future research in this field. A systematic and comprehensive search of iminosugars-related literature published from 1993 to 2022 was conducted using the Scopus database and the bibliometric R-package was used for the analysis of bibliometric information. The analysis revealed that the annual growth rate for the published articles on iminosugars is 12.93% and shows a growing trend since 2003 with France as the country with the highest number of published papers (490 documents). The most frequent authors' keyword used in studies related to iminosugars is drug synthesis (301 times). This valuable information is crucial as it provides a platform for the progression of knowledge in this field.

Keywords: Bibliometric; iminosugars; pyrrolidine; glycosidase; inhibition

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Iminosugars are structural analogs of sugar where the ring oxygen atom of sugar is replaced by a nitrogen atom [1]. The first natural iminosugars, nojirimycin, and its reduced form, 1-deoxynojirimycin (DNJ) were discovered in 1967 and the first iminosugars-based drug under the trade name Glyset™ have been commercialized in 1996, which took years after it was first discovered [2]. Iminosugars are well-known potent glycosidase inhibitors as well as potent inhibitors for various enzymes. Numerous structures of iminosugars were studied for the treatment of type II diabetes [3] and this has been an important topic of study in the literature for many years. Type II diabetes is non-insulin-dependent diabetes that mainly results from poor diet and social habits. One of the therapeutic approaches to treat diabetes is to retard the absorption of glucose via inhibitors of enzymes such as α-glucosidase and α-amylase which these enzymes delay the absorption of carbohydrates (sugar) ingested but in return cause bloating and flatulence [4].

Over the past five decades, it was realized that inhibitors of these enzymes, such as DNJ could be used therapeutically in the oral treatment of type II diabetes. The drawback of compounds such as DNJ with no anomeric substituent is the lack of selectivity towards the different types of glycosidases (α and β) [5], and this initiated synthetic approaches to produce derivatives with enhanced activity. The second generation iminosugars-based drugs, represented by novel iminosugars i.e acarbose and miglitol with enhanced potency and higher specificity have emerged because of the undesired effects of the first-generation iminosugars-based drugs [6]. Furthermore, very few changes in the stereochemistry or structure of iminosugars such as functional group variations, alter their specificity and potency [7].

As a result, several reviews on iminosugars have been reported [6,8] to facilitate scholars to understand and organize findings from the literature. Nonetheless, these reviews are typically qualitative and not replicable. In contrast, bibliometric analysis has the potential to provide a reproducible and systematic approach to the analysis of literature [9]. Bibliometric analysis is also appropriate for identifying the knowledge in a particular area and the evolution of topics [10]. Responding to the limited quantitative literature approaches on iminosugars, this work aims to conduct a bibliometric analysis of literature related to iminosugars as published in the Scopus online database as of December 2022. This paper presents the first bibliometric analysis of iminosugars-related studies and covers the aspects of the document type, year of publication, source of publication, authorship, keywords, and countries. This work warrants a better understanding of the current and latest trends in this field of study.

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METHOD

The analysis of the literature was performed using the Scopus database. As stated by [11], "Scopus includes most of the journals indexed in Web of Science (WoS)". Thus, the selected database is reliable. The searched keyword used was "imino-sugars*" based on the article title. There was a total of 497 articles retrieved from the database which included all types of publications published in Scopus from 1993 to 2022. The data were retrieved on 6th December 2022. The bibliometric R-packages and VOSviewer were used for the analysis of bibliometric information [12]. The analysis was presented in tables and figures by focusing on the top 10 most relevant contributions.

RESULTS AND DISCUSSION

Analysis of Document Type

Document type is a document based on the originality of the document either article, book, book chapter, conference paper, letter, etc. [9]. The works published on iminosugars were categorized into nine document types (Table 1). The article dominated the sources of publications with 428 documents (86.10%) and only 35 documents (7.04%) representing the review paper. Book chapters contributed 3.62% (18 documents) and other types of documents contributed less than 2% to the total number of publications. This indicates publishing a review paper in this research area is moderately assuring because the ratio of a review paper to an article is below average (0.083). However, this could also be assumed as an opportunity as the classification of a publication as a review or an article is sometimes debatable because some documents labeled as articles were review papers and vice versa [13].

Analysis of Publication by Year and Annual Growth

Figure 1 summarizes the detailed statistics of publications published by year on iminosugars from 1993 to 2022. The number of published documents signifies the scientific activity [13]. As in Scopus records, the first article published on iminosugars was authored by Jacob and Bryant who investigated the potential of iminosugars for the treatment of HIV [14]. The annual growth of the publication showed no significant increment for a few years after the first publication in 1993 until it started showing an increasing pattern in 2003 due to the exploration of iminosugars derivates and their structure modifications to enhance their glycosidase inhibition potential. During the highly active period between 2008 to 2016 with publications of more than 20 documents per year, the top record was observed in 2016, with a total of 38 documents. The slope between 2017 to 2018 occurred because studies revealed only a proportion of iminosugars were reported as potent glycosidase inhibitors [6]. The discovery of other therapeutic potentials of imino-sugars including anticancer and antiviral sparked the rise from 2019 to 2022. Overall, the annual growth in the field of study was 12.93%. This suggests the growing interest in iminosugars-related studies due to their substantial therapeutic applications.

Table 1. The document types and frequency of publication published from 1993 to 2022 in iminosugars-related studies retrieved from the Scopus database.

Document types	No. of publication	%
Article	428	86.10
Review	35	7.04
Book chapter	18	3.62
Conference paper	6	1.21
Erratum	5	1.01
Note	2	0.40
Letter	1	0.20
Book	1	0.20
Short survey	1	0.20

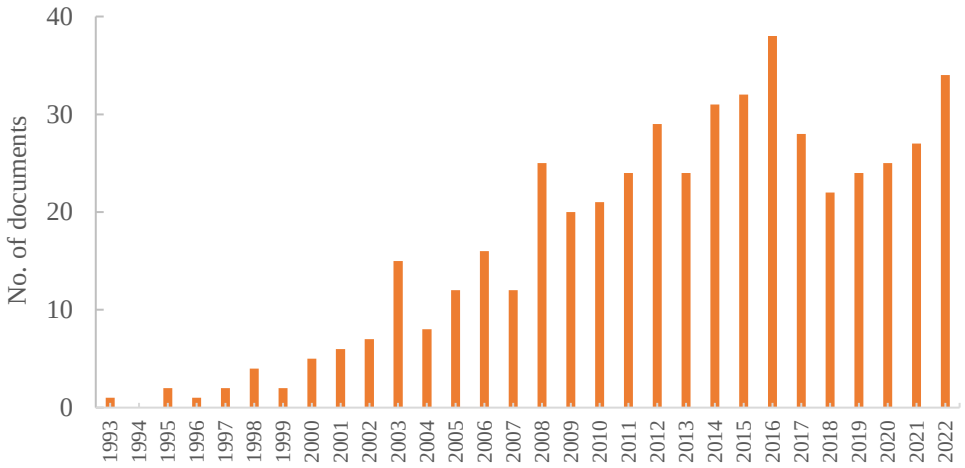

Figure 1. Publication published by year from 1993 to 2022 in iminosugars-related studies retrieved from the Scopus database (Data retrieved in December 2022).

Analysis of Most Relevance Sources

The articles on iminosugars had been published in 148 different journals. The top 10 most productive scientific journals on iminosugars were tabulated in Table 2. The most productive journals with more than 20 publications were The Journal of Organic Chemistry, Organic and Biomolecular Chemistry, Tetrahedron Letters, Carbohydrates Research, The European Journal of Organic Chemistry, and Organic Letters. These reflected the subject area of these journals which is organic chemistry. In addition, the first publication in iminosugars research area was published in Tetrahedron Letters in 1995, and years later in 2000, The Journal of Organic Chemistry published its first article and was constantly productive within the study period. The analysis also revealed that 50% of the top 10 journals have an h-index higher than 10 which indicated that the works on iminosugars were published in high h-index journals. Moreover, based on Journal Impact Factor (JIF) 2021, one journal was categorized in the 3rd quartile journals (Carbohydrate Research) while others were listed either in the 1st quartile or 2nd quartile journals. Meanwhile, only tetrahedron Asymmetry was assigned without a JIF.

Table 2. Top 10 most productive scientific journals in iminosugars-related studies.

Top 10 Sources	No. of publication	h-index
Journal of Organic Chemistry	26	19
Organic and Biomolecular Chemistry	26	13
Tetrahedron Letters	24	14
Carbohydrate Research	22	9
The European Journal of Organic Chemistry	21	11
Organic Letters	20	15
Bioorganic and Medicinal Chemistry	17	13
Tetrahedron Asymmetry	17	13
Chemistry - A European Journal	12	9
Molecules	12	4

Table 3. Top 10 most globally cited documents in iminosugars-related studies.

Documents	Total Citations	Document Type
Compain P, 2008; DOI: 10.1002/9780470517437 [16]	553	book
Pavlovic V, 2003; DOI: 10.1073/pnas.1031527100 [21]	308	articles
Horne G, 2011; DOI: 10.1016/j.drudis.2010.08.017 [19]	283	review
Nash RJ, 2011; DOI: 10.4155/fmc.11.117 [17]	242	review
Ichikawa Y, 1998; DOI: 10.1021/ja973443k [22]	223	article
Greimel P, 2003; DOI: 10.2174/1568026033452456 [20]	214	review
Compain P, 2003: DOI: 10.2174/1568026033452474 [18]	210	review
Cox TM, 2003: DOI: 10.1023/A:1025902113005 [23]	208	article
Wu SF, 2002: DOI: 10.1128/JVI.76.8.3596-3604.2002 [24]	198	article
Compain P, 2010: DOI: 10.1002/anie.201002802 [25]	186	article

Analysis of Most Relevance Publications

Table 3 discloses the top 10 documents with the highest number of global citations up until December 2022. Global citations measure the impact of a document on the whole bibliographic database [15]. Among the 497 documents retrieved, the document with the highest citation was a book authored by Compain P., *Iminosugars: From Synthesis to Therapeutic Applications* [16]. This book is a collection of research papers on the synthesis of iminosugars and their therapeutic functions. Nash and co-workers [17] and Compain P. [18] reviewed the synthetic routes of iminosugars derivatives, and the other review papers focused on the clinical studies of iminosugars [19,20]. Meanwhile, the published documents under the category of article explored the synthesis of iminosugars and their antiviral potential as well as their most promising biological properties as alpha and beta-glucosidase inhibitors [21-25]. Nonetheless, the analysis summarized that both the review and research papers were equally significant. In addition, the duration of the publication's availability, the quality of the papers, and the types of documents determine their high citation value [12].

Analysis of Most Relevance Authors

The research papers on iminosugars involved 1539 authors in total, among which 1475 authors published less than five papers, 26 authors with 6–9 papers, and 38 authors published more than 10 papers. From the perspective of total publication (Table 4), the top three authors are Compain P, Kato A, and Flett GWI, with 35 articles, 35 articles, and 24 articles, respectively. Among the top 10 of the most influential authors on iminosugars-related studies, Compain P was ranked first. Compain P's h-index and g-index are 20 and 35, respectively. The h-index tends to be higher depending on the period in which the articles have been available [12].

Table 4. Top 10 most influential authors in iminosugars-related studies.

Authors	h-index	g-index	Total publication	Production year start
Compain P	20	35	35	2000
Kato A	17	31	35	2005
Fleet GWI	16	23	24	2005
Zitzmann N	16	22	22	2001
Martin OR	14	19	19	2000
Ortiz Mellet C	14	22	22	2010
García Fernández JM	13	21	21	2008
Adachi I	12	13	13	2005
Dwek RA	12	16	16	2001
Nash RJ	12	18	18	2007

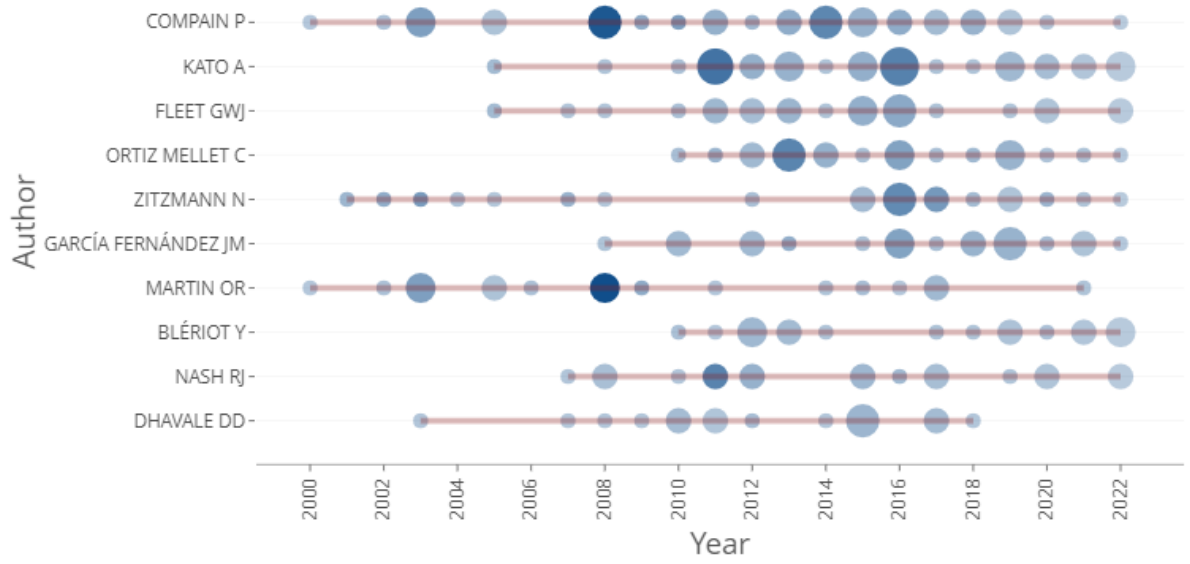

Figure 2. Authors' production over time in iminosugars-related studies.

As can be seen from Figure 2, the colour of the circle represented the number of citations, and the size of the circle indicated the number of publications [26]. Compain P. has started to publish articles since 2000, with the largest number of published papers and the highest frequency of average citations per item in 2008. All the top three authors, Compain P, Kato A, and Flett GWI actively published papers starting from 2010.

Analysis of Authors' Keywords

The analysis of keywords used by authors was performed using VOSviewer software. Figure 3 shows the leading keywords used by authors and these keywords represent the content of their research works. As shown in the figure, the most frequent keywords used by authors are drug synthesis and synthesis with frequencies of 301 and 277, respectively. Studies in this area primarily focused on the synthesis route of iminosugars and their derivatives together with the inhibition potential mainly as glycosidase inhibitors. The terms stereo-chemistry and chemistry were relatable to term synthesis since structure modification could lead to enhancing the inhibition potential of iminosugars and their derivatives. The terms human and animal outnumbered metabolism because in vivo and in vitro studies were conducted to justify the clinical functions of drug-based iminosugars. The proven drugs will then be further investigated to identify their metabolic pathways. 1-deoxynojirimycin (DNJ) also appears as one of the frequent keywords because it was the first synthesized iminosugars and several works were performed on its structure modification. The most noteworthy finding is that pyrrolidine and piperidine emerge as significant keywords among other classifications of iminosugars, indicating that these molecules are the focus of interest.

Analysis of Countries' Scientific Production

Considering the authors' countries, the selected documents originated from 31 countries worldwide. The countries contributing to the productivity of scientific publications in the iminosugars research area are shown in Figure 4. The top country was France with a total of 490 publications followed by Spain and The United Kingdom (UK) with total publications of 399 and 338, respectively. Among the top 10 countries, there are three Asian countries in descending order, China (326 publications), Japan (282 publications), and India (267 publications). Interestingly, authors from Japan have productively published articles on iminosugars since 1995. To some extent, such information is vital in determining the influence and importance of countries in the iminosugars research area.

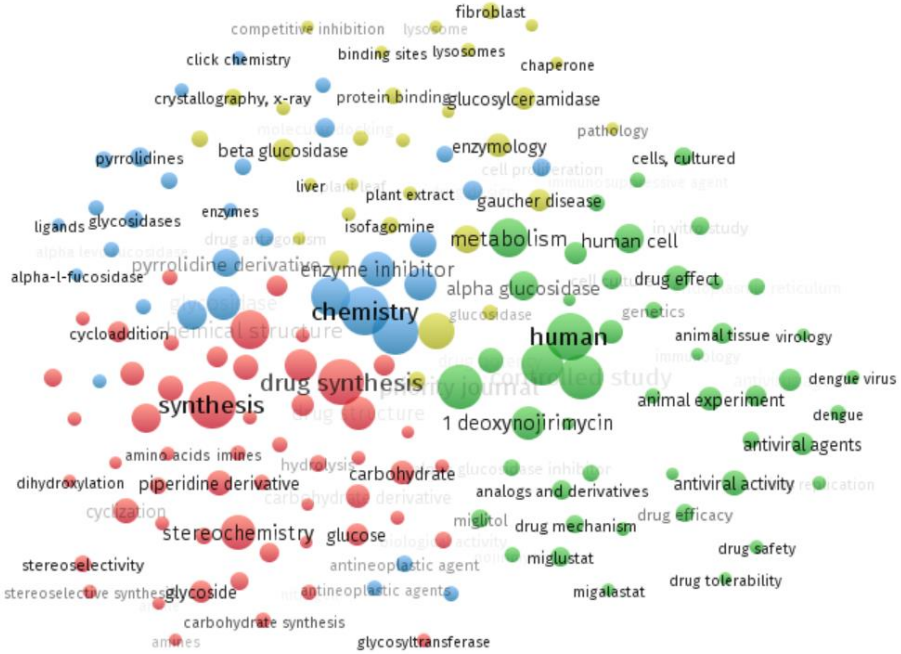

Figure 3. Visualization of keywords used by authors in iminosugars-related studies.

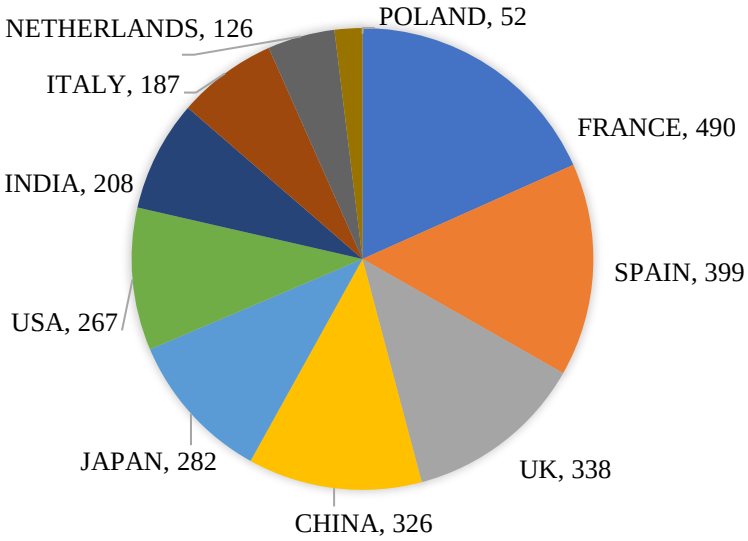

Figure 4. Top 10 countries' scientific production in iminosugars-related studies.

CONCLUSION

In this study, 497 documents had been retrieved from the Scopus database as of 6th December 2022. The analysis of the database was performed using R-packages and Vosviewer. Research in iminosugars-related works suggested the following characteristics:

From the perspective of the document type, the article was the most frequently published document with a percentage of more than 86.1%. This indicates that publishing a research article is the main interest of scholars in the field of iminosugars-related studies. As for the publication trend, it demonstrated an increasing pattern starting from 2003 even though between 1993 to 2002 the growth rate was slow. However, the publication's annual growth rate (12.93%) shows a promising increasing trend in the future. Meanwhile, data mining and analysis on the most relevant documents illustrate that the most globally cited documents in iminosugars-related studies were published in high h-index journals.

The most influential authors in the studies related to iminosugars were Compain P, Kato A, and Flett GWI. The most frequently used keywords were

drug synthesis, synthesis, stereochemistry, human, animal, metabolism, DNJ, pyrrolidine, and piperidine. In terms of authors' countries, France was on the top chart followed by UK and China. This information is equally important, particularly for young researchers.

Nonetheless, there are several limitations in this work. Firstly, the searched keywords used catered to all article titles with iminosugars term which covers a broad range of study area. Adding to this, a detailed analysis from another perspective could be performed. Despite these limitations, our work is the first bibliometric analysis report on studies related to iminosugars by exploiting data from the Scopus database. The outcomes presented in this paper may facilitate novice researchers in their future work.

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REFERENCE

1. Wadood, A., Ghufran, M., Khan, A., Azam, S. S., Jelani, M. and Uddin, R. (2018) Selective glycosidase inhibitors: A patent review (2012–present). *International Journal of Biological Macromolecules*, **111**, 82–91 (January).

2. Compain, P., Chagnault, V. and Martin, O. R. (2009) Tactics and strategies for the synthesis of iminosugar C-glycosides: A review. *Tetrahedron Asymmetry*, **20(6–8)**, 672–711.

3. Yang, Y. and Yu, B. (2017) Recent advances in the chemical synthesis of C-glycosides. *Chemical Reviews*, **117(19)**, 12281–12356.

4. Kerru, N., Singh-Pillay, A., Awolade, P. and Singh, P. (2018) Current anti-diabetic agents and their molecular targets: A review. *European Journal of Medicinal Chemistry*, **152**, 436–488.

5. Cipolla, L., La Ferla, B. and Nicotra, F. (2005) General methods for iminosugar synthesis. *Current Topics in Medicinal Chemistry*, **3(5)**, 485–511.

6. Esposito, A., Alonzo, D. D., Fenza, M. De, Gregorio, E. De, Tamanini, A., Lippi, G., Dechecchi, M. C. and Guaragna, A. (2020) Synthesis and therapeutic applications of imino-sugars in cystic fibrosis. *International Journal of Molecular Sciences*, **21**, 1–34.

7. Faisca Phillips, A. M., Guedes da Silva, M. F. C. and Pombeiro, A. J. L. (2020) The stereoselective nitro-mannich reaction in the synthesis of active pharmaceutical ingredients and other biologically active compounds. *Frontiers in Chemistry*, **8**, 1–27 (January).

8. Dragutan, I., Dragutan, V., Mitan, C., Vosloo, H. C. M., Delaude, L. and Demonceau, A. (2011) Metathesis access to monocyclic iminocyclitol-based therapeutic agents. *Beilstein Journal of Organic Chemistry*, **7**, 699–716.

9. Ahmi, A. and Mohamad, R. (2019) Bibliometric analysis of global scientific literature on web accessibility. *International Journal of Recent Technology and Engineering*, **7(6S2)**, 250–258.

10. Oshodi, O. S., Awuzie, B. O., Akotia, J., Ademiloye, A. S. and Ngowi, A. (2020) A bibliometric analysis of recycled concrete research (1978–2019). *Built Environment Project and Asset Management*, **10(5)**, 725–736.

11. Secinaro, S. and Calandra, D. (2021) Halal food: structured literature review and research agenda. *British Food Journal*, **123(1),** 225–243.

12. Weinand, J. M. (2020) Reviewing municipal energy system planning in a bibliometric analysis: Evolution of the research field between 1991 and 2019. *Energies*, **13(1367)**, 1–18.

13. Manuelian, C. L., Penasa, M., da Costa, L., Burbi, S., Righi, F. and Marchi, M. D. (2020) Organic livestock production: A bibliometric review. *Animals*, **10**, 1–16.

14. Jacob, G. S. and Bryant, M. L. (1993) Iminosugars glycosylation inhibitors as anti-HIV agents. *Perspectives Drug Discovery and Design*, **1(1)**, 211–224.

15. Aria, M and Cuccurullo, C. (2017) Bibliometrix: An R-tool for comprehensive science mapping analysis. *Journal of Infometrics*, **11**, 959–975.

16. Compain, P. and Martin O. R. (2008) Iminosugars: From synthesis to therapeutic applications. *John Wiley & Sons Ltd., New York.*

17. Nash, R. J., Kato, A., Yu, C. Y. and Fleet, G. W. (2011) Iminosugars as therapeutic agents: Recent advances and promising trends. *Future Medicinal Chemistry*, **3(12)**, 1513–1521.

18. Compain, P., Martin, O.R. and Godin, G. (2003) General access to iminosugar C-glycoside building blocks using cross-metathesis: A gateway to glycoconjugate mimetics. *Organic Letters*, **5(18)**, 3269–3272.

19. Horne, G., Wilson, F. X., Tinsley, J., Williams, D. H. and Storer, R. (2011) Iminosugars past, present and future: Medicines for tomorrow. *Drug Discovery Today*, **16(3–4)**, 107–118.

20. Greimel, J., Spreitz, A. E. S. and Wrodnigg, T.

M. (2003) Iminosugars and relatives as antiviral and potential anti-infective agents. *Current Topics in Medicinal Chemistry*, **3(5)**, 513–523.

21. Pavlovic, D., Neville, D. C. A., Argaud, O., Blumberg, B., Dwek, R. A. and Zitzmann, N. (2003) The hepatitis C virus p7 protein forms an ion channel that is inhibited by long-alkyl-chain iminosugar derivatives in *Proceedings of the National Academy of Sciences, United Kingdom*, **100(10)**, 6104–6108.

22. Ichikawa, Y., Igarashi, Y., Ichikawa, M. and Suhara, Y. (1998) 1-*N*-Iminosugars: Potent and selective inhibitors of β-glycosidases. *Journal of the American Chemical Society*, **120(13)**, 3007–3018.

23. Cox, T. M., Aerts, J. M. F. G., Andria, G., Beck, M., Belmatoug, N., Bembi, B., Chertkoff, R., Vom Dahl, S., Elstein, D., Erikson, A., Giralt, M., Heitner, R., Hollak, C., Hrebicek, M., Lewis, S., Mehta, A., Pastores, G. M., Rolfs, A., Sa Miranda, M. C. and Zimran, A (2003) The role of the iminosugar N-butyldeoxynojirimycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease: A position statement. *Journal of Inherited Metabolic Disease*, **26(6)**, 513–526.

24. Wu, S. F., Lee, C. J., Liao, C. L., Dwek, R. A., Zitzmann, N. and Lin, Y. L. (2002) Antiviral effects of an iminosugar derivative on flavivirus infections. *Journal of Virology*, **76(8)**, 3596–3604.

25. Compain, P., Decroocq, C., Iehl, J., Holler, M., Hazelard, D., Barragán, T. M., Mellet, C. O. and Nierengarten, J. F. (2010) Glycosidase inhibition with fullerene iminosugar balls: A dramatic multivalent effect. *A Journal of The German Chemical Society*, **49(33)**, 5753–5756.

26. Xie, H., Zhang, Y., Wu, Z. and Lu, T. (2020) A bibliometric analysis on land degradation: Current status, development, and future directions. *Landscape Ecology*, **9(1)**, 1–37.